

Electronic Supplementary Information

The ring opening reaction of 1, 3-dithiol-2-one systems is fully reversible

Ashta Chandra Ghosh,^a Jakob Klaus Reinhardt,^a Markus Karl Kindermann,^a Carola Schulzke^{*a}

^a*Institut für Biochemie, Ernst-Moritz-Arndt-Universität Greifswald, Felix-Hausdorff-Strasse 4, 17487 Greifswald, Germany. Fax: +49 3834 864377;
Tel: +49 3834 864321; E-mail: carola.schulzke@uni-greifswald.de*

Table of Contents

1. General experimental details
2. Synthesis and characterization data of compounds **1**, **2**, **2'** and **3**
3. ¹H-NMR and ¹³C-NMR spectra of compounds **1**, **2**, **2'** and **3** (**S1** to **S7**)
4. Infrared spectra of compounds **2**, **2'** and **3** (**S8** to **S10**)
5. UV-Vis spectra of compounds **2**, **3** and **2'**
6. DFT calculation for proposed mechanism
7. References

Experimental Section

Materials and methods: All materials were purchased from Sigma Aldrich and abcr and were used without further purification. NMR measurements were recorded on a Bruker Avance II-300 MHz instrument. All samples were dissolved in deuterated solvents and Chemical shifts (δ) are given in parts per million (ppm) using solvent signals as the reference (CDCl_3 ^1H : $\delta = 7.24$ ppm; ^{13}C : $\delta = 77.0$ ppm) related to external tetramethylsilane ($\delta = 0$ ppm). Coupling constants (J) are reported in Hertz (Hz) and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), spt (septet), m (multiplet), dd (doublet of doublet). High resolution mass spectrometry (HRMS) analyses were carried out on a Water-Micromass Q-TOF hybrid mass spectrometer equipped with an orthogonal electrospray source (z-sprey) by Muhammad Zubair at Trinity College in Dublin. This was operated in an electrospray positive ion mode (ESI^+) or electrospray negative ion mode (ESI^-). All infrared spectra were recorded ($4000\text{--}400\text{ cm}^{-1}$) on a Perkin-Elmer Fourier-Transform Infrared (FTIR) spectrophotometer as KBr pellets. Elemental analyses (C, H, N and S) were carried out with an Elementar vario micro elemental analyzer. UV-Vis measurements were carried out on a Shimadzu 3600 instrument with the concentration of 5×10^{-5} M and 2×10^{-3} M in MeOH as solvent for the ligand and KOH respectively.

Synthesis of for O-isopropyl S-3-oxobutan-2-yl dithiocarbonate (1)¹: O-isopropylxanthate (3,48 g, 20 mmol) dissolved in 100 mL dry acetone was slowly added to a solution of 3-bromobutane-2-one (2 mL, 2,88 g, 19,1 mmol) in 40 mL dry acetone. The mixture was stirred for 1 h at r.t. and then solvent was removed in vacuum. The residue was dissolved in water and was extracted two times with Et_2O . The organic phases were combined, dried over Na_2SO_4 and the solvent was evaporated on a rotary evaporator at 40°C yielding a yellow liquid consisting of O-isopropyl S-3-oxobutan-2-yl carbonodithioate. Yield: 3.86g (94%). ^1H NMR (300 MHz, CDCl_3) δ (ppm) = 1,4 (d, $J=6,2$ Hz, 6H), 1,47 (d, $J=7,2$ Hz, 3H), 2,31 (s, 3H), 4,38 (q, $J=7,2$ Hz, 1H), 5,73 (spt, $J=6,2$ Hz, 1H).

Synthesis of 4, 5-dimethyl-1,3-dithiol-2-ones (2)²: Compound 1 (3.86 g, 18.7 mmol) was slowly added to a soln of concd H_2SO_4 (100 mL) that had been pre-cooled in an ice-salt bath. The resulting soln was stirred for 30 min, the ice-salt bath was removed, and the solution was stirred for a further 90 min. This soln was cooled in an ice bath and slowly poured into ice-cooled

H₂O (400 mL). After stirring for 15 min, the solution was extracted with CH₂Cl₂ (3 × 50 mL), dried over Na₂SO₄ and concentrated on a rotary evaporator to produce crude, dark red oil that is purified by short-path vacuum distillation at 65-70 °C and 0,56 mbar pressure to afford 2.32 g (85%) of 4, 5-dimethyl-1,3-dithiol-2-ones as very pale yellow oil. The freshly prepared pale yellow oil was dissolved in warm hexane followed by cooling at -20 °C to get white colored single crystal and the structure was confirmed by single crystal X-ray crystallography according to literature^{2b}. ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 2.15 (s, 4H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 13.60, 122.71, 191.91 ppm. IR (KBr): 3447, 3245, 2945, 2911, 2847, 1754, 1657, 1602, 1446, 1391, 1187, 1098, 948, 883, 753 cm⁻¹. EI-MS: *m/z* 146.7. Elemental analysis for C₅H₆OS₂: C, 41.07; H, 4.14; S, 43.86. Found: C, 40.46; H, 4.03; S, 44.41.

Synthesis of 2, 3-dimethyl-1,4 dithiolate (3): 0.0584 g (0.4 mmol) of 4, 5-dimethyl-1,3-dithiol-2-ones and 0.056 g (2.5 equ., 1 mmol) of potassium hydroxide was taken in a Schlenk flask under nitrogen atmosphere. 3 mL deuterated methanol was added to the flask and the mixture was stirred for 2h. The solution was turned to light yellow color indicating the deprotection of the ring. Then 1 mL of the above solution was taken for NMR measurement. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.17(s, 4H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 161.3, 158.0, 132.9, 124.3 and 13.6. IR (KBr): 3404, 3228, 2965, 2922, 2866, 1649, 1463, 1375, 1310, 1191, 1085, 913, 833 cm⁻¹.

Synthesis of 4, 5-dimethyl-1,3-dithiol-2-ones (2'): To the remaining 2mL solution potassium dithiolate salt (3) conc. HCl (56 μL, 2.5 equ., 1mmol) was added and the mixture was stirred for another 1h. Then the mixture was filtered to remove the white precipitate of KCl and the filtrate was concentrated and submitted for ¹H, ¹³C NMR. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.15(s, 4H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 192.1, 122.8 and 13.7. IR (KBr): 3440, 3255, 2978, 2915, 2856, 1750, 1653, 1603, 1438, 1369, 1191, 1097, 885, 750 cm⁻¹.

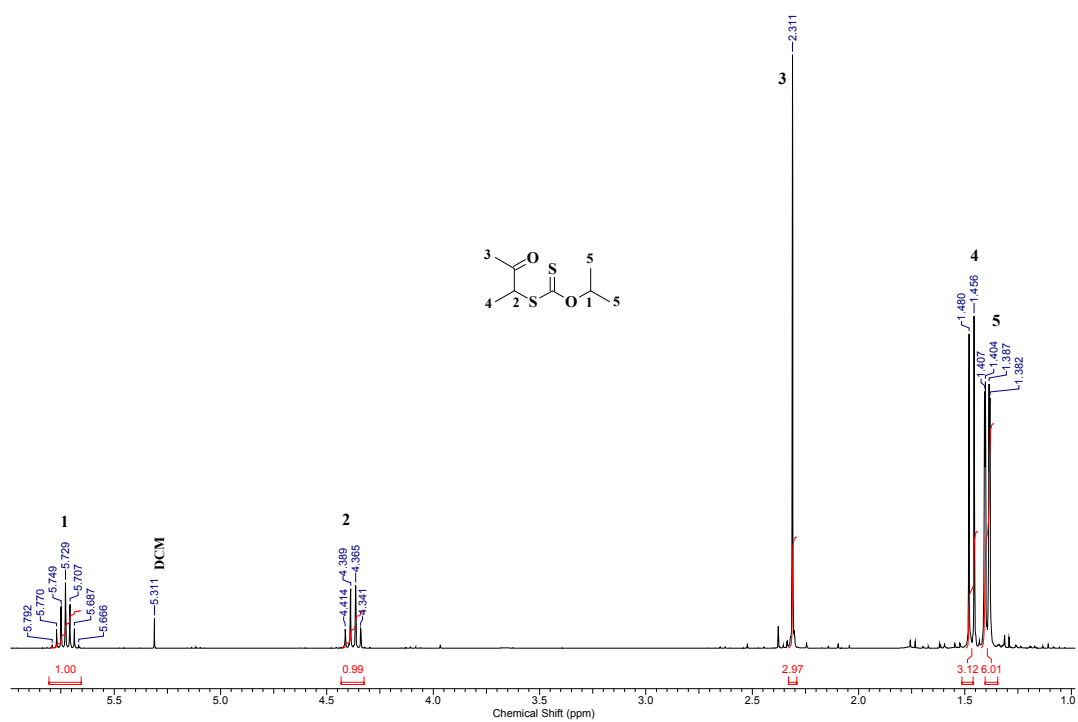


Figure S1. ^1H NMR spectra of O-isopropyl S-3-oxobutan-2-yl dithiocarbonate (**1**).

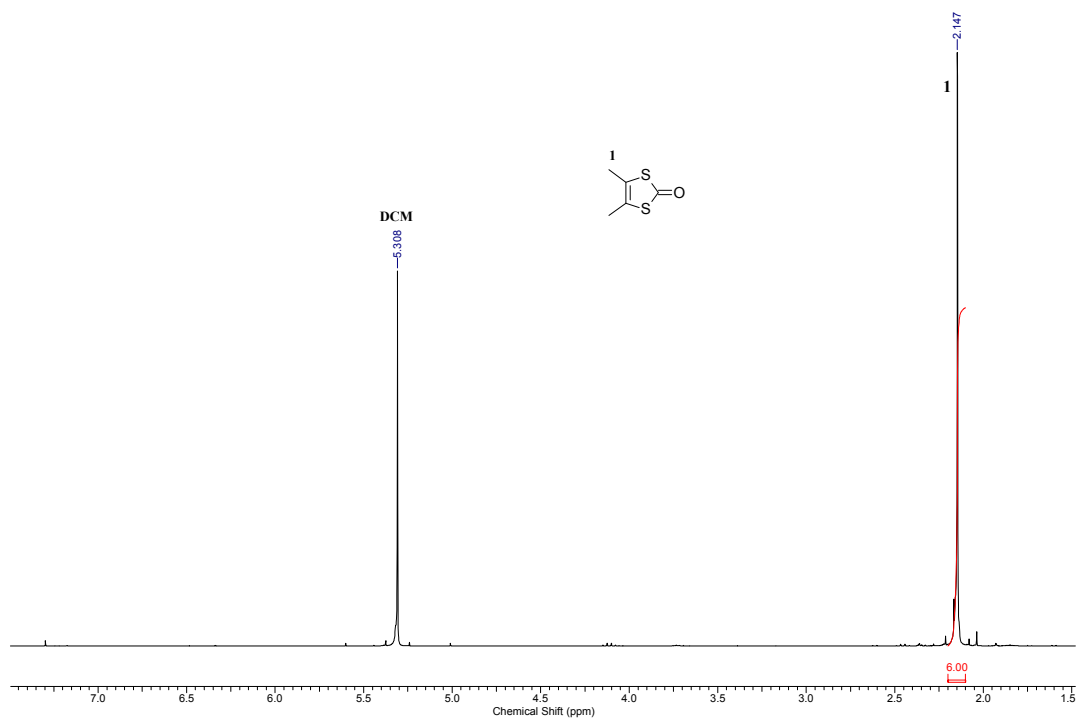


Figure S2. ^1H NMR spectra of 4, 5-dimethyl-1,3-dithiol-2-ones (**2**).

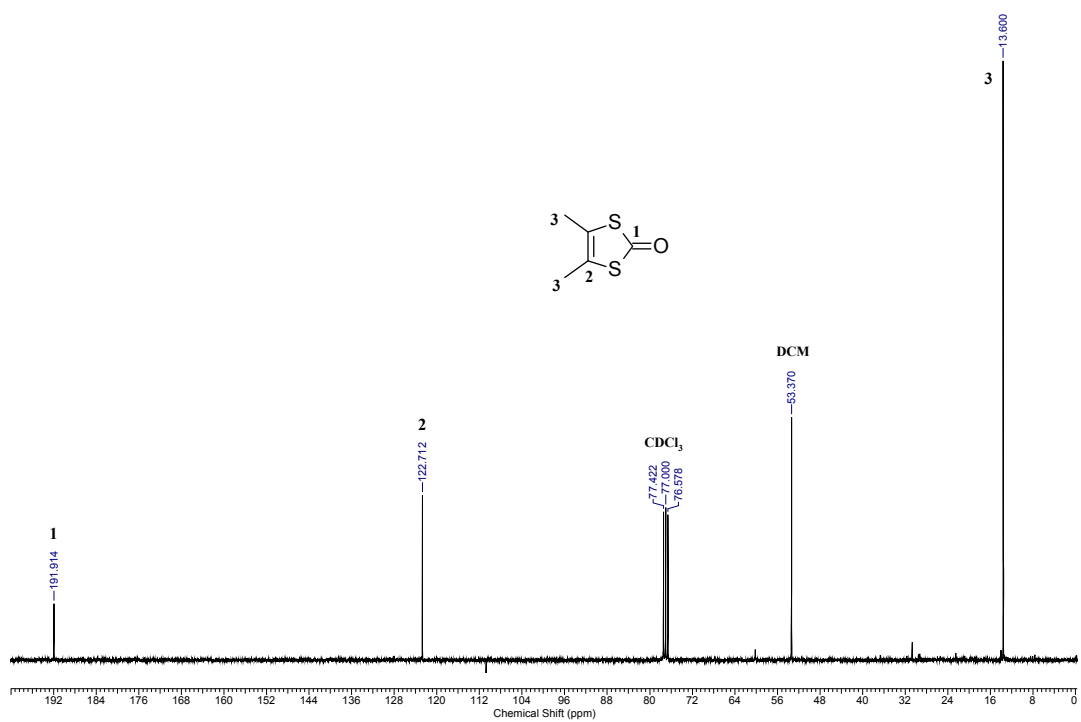


Figure S3. ¹³C NMR spectra of 4, 5-dimethyl-1, 3-dithiol-2-ones (**2**).

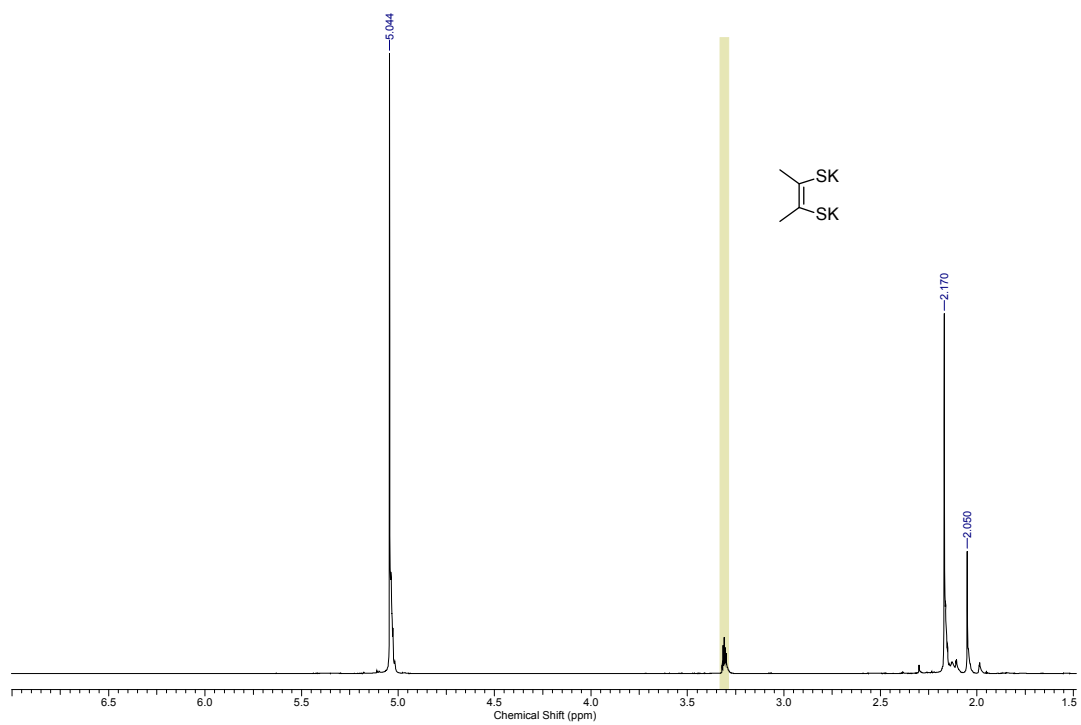


Figure S4. ¹H NMR spectra of 2, 3-dimethyl-1, 4 dithiolate (**3**).

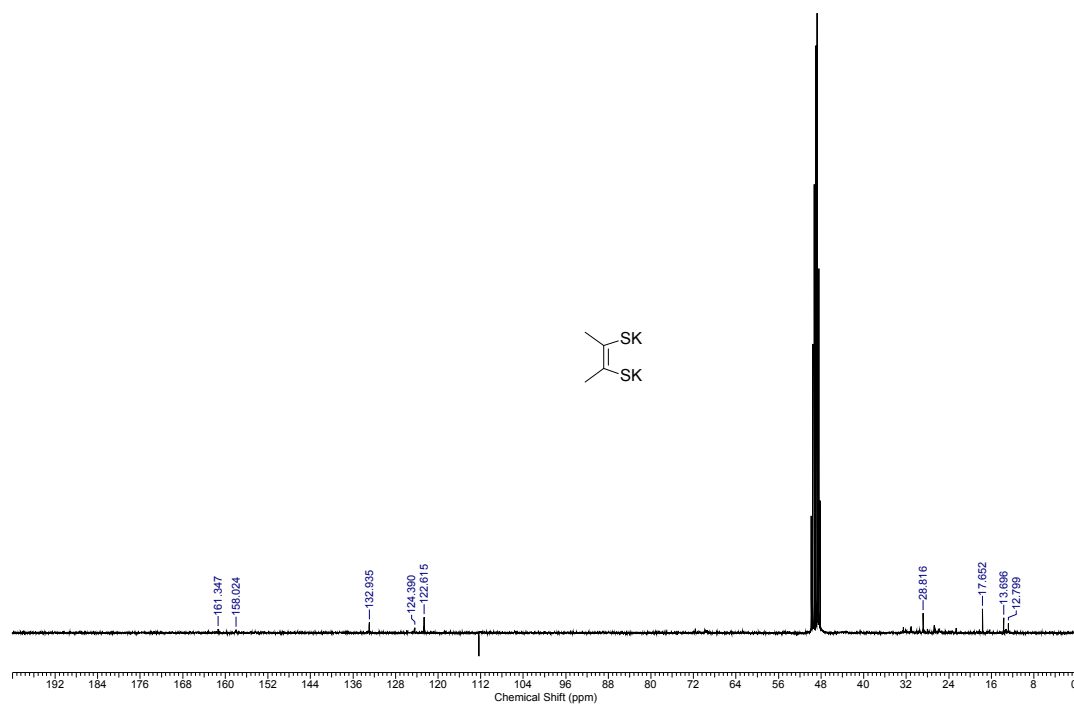


Figure S5. ^{13}C NMR spectra of 2, 3-dimethyl-1, 4 dithiolate (**3**).

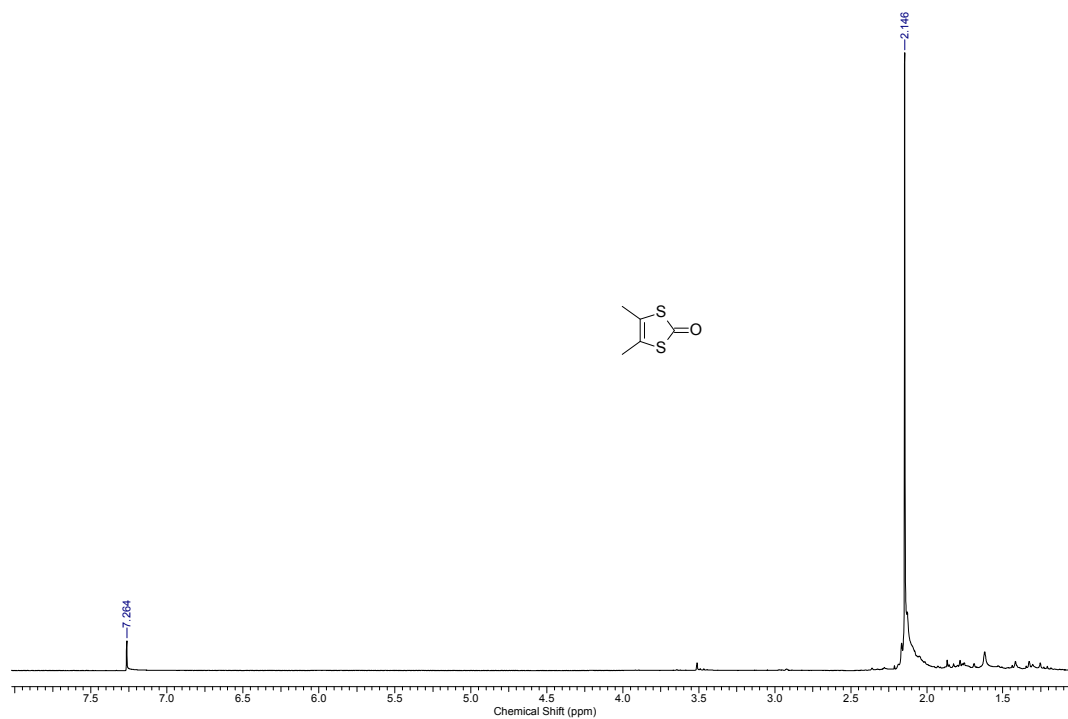


Figure S6. ^1H NMR spectra of 4, 5-dimethyl-1,3-dithiol-2-ones (**2'**).

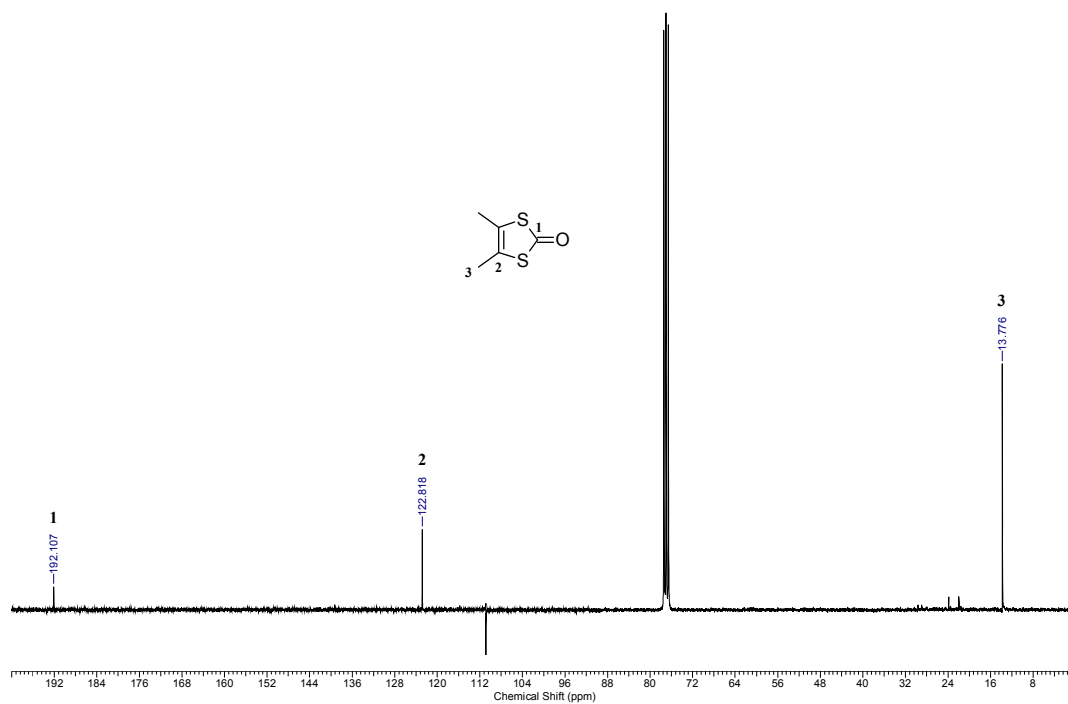


Figure S7. ^{13}C NMR spectra of 4, 5-dimethyl-1,3-dithiol-2-ones (**2'**).

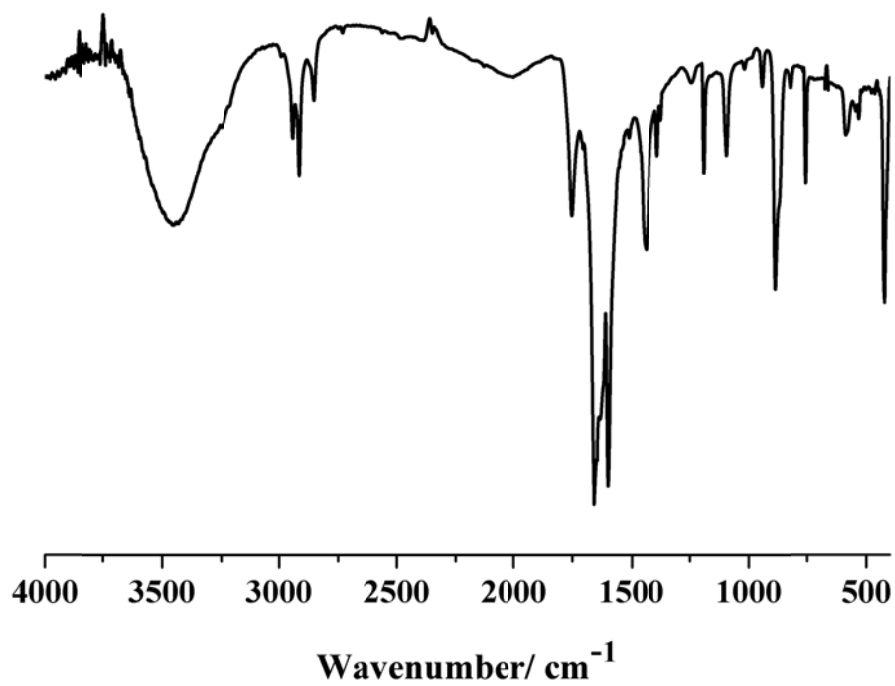


Figure S8. IR spectrum of **2** recorded in KBr Pellets.

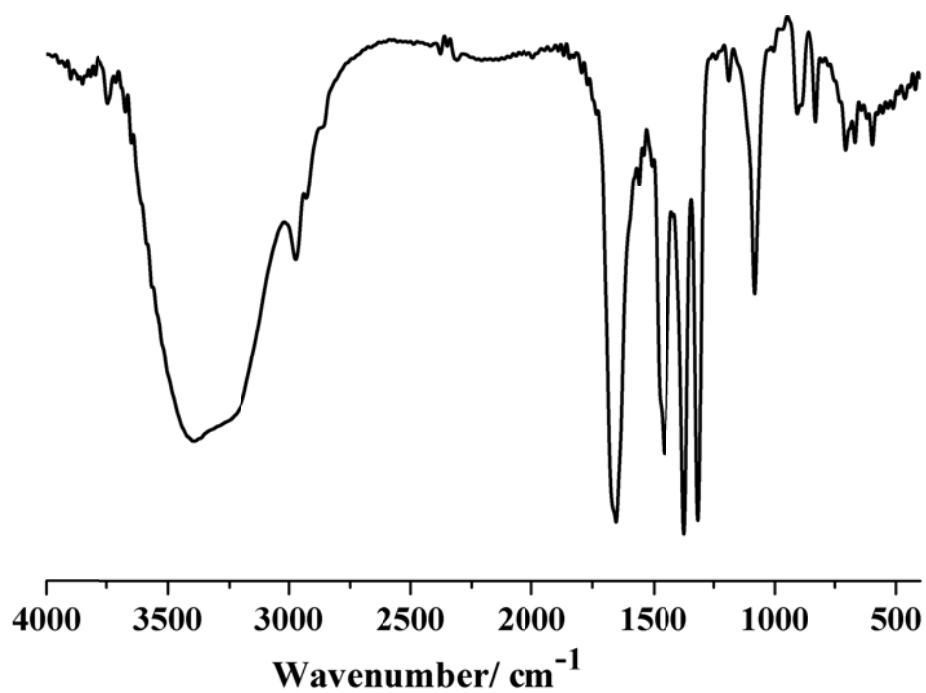


Figure S9. IR spectrum of **3** recorded in KBr Pellets.

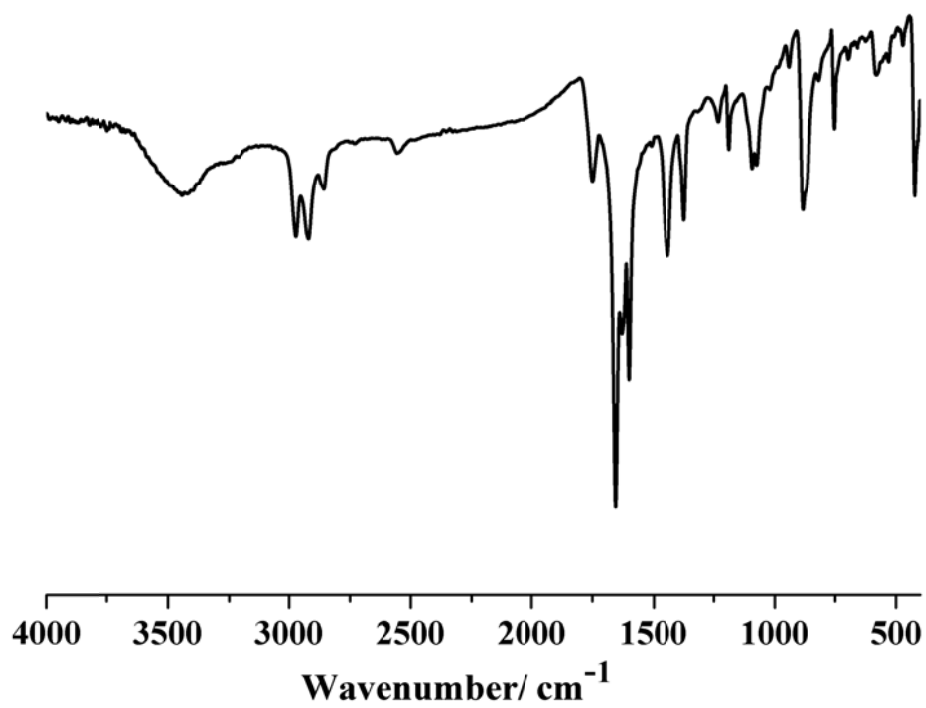


Figure S10. IR spectrum of **2'** recorded in KBr Pellets.

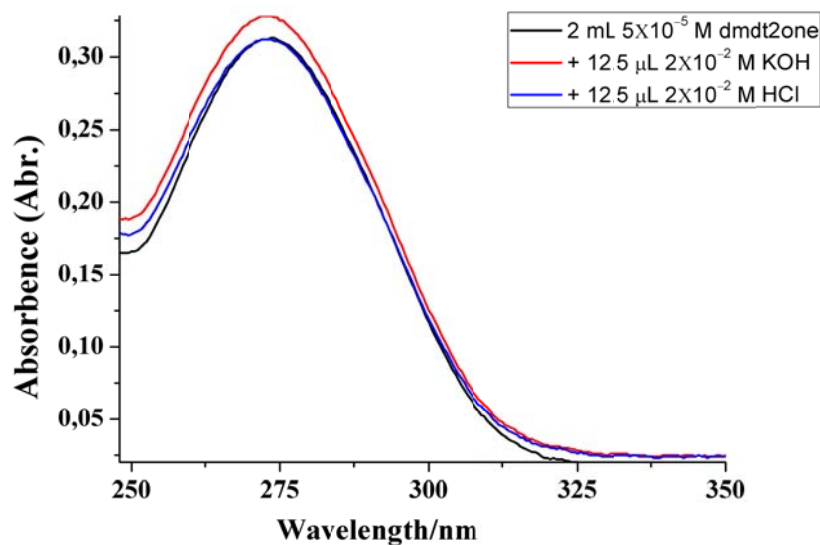


Figure S11. Absorbance spectra of 4, 5-dimethyl-1,3-dithiol-2-ones (**2**) (black); 2, 3-dimethyl-1, 4 dithiolate (**3**) (red) and 4, 5-dimethyl-1,3-dithiol-2-ones (**2'**) (blue) in CH₃OH as solvent.

DFT calculation for the proposed mechanism: For a better understanding of the proposed mechanism of ring opening-closing reversibility in 1,3-dithiol-2-one systems, we carried out ab initio calculations.

The calculations were done with the B3LYP/6-311+G** basis set to properly treat the sulfur d-orbitals. The geometries of reactants and products after complete addition of base have been optimized and the full optimization was verified with a frequency calculation. Since we were concerned with the understanding of the mechanism only, no additional H₂O molecules were included in the calculations and no solvation models (eg, Tomasi's Polarized Continuum Model (PCM)³) are considered since experimental studies were partly carried out in different solvents.

An attempt was made to elucidate whether it is a concerted mechanism or a multi-step process taking place. The search for a transition state (TS) that belongs to a concerted mechanism (simultaneous addition of two OH⁻ ions to the 4,5-dimethyl-1,3-dithiol-2-one and formation of 1,3-dithio-dianion plus free carbonic acid (H₂CO₃), or the reversible attachment of H₂CO₃ to the 2,3-dimethyl-1,4-dithiobut-2-en-dianion with simultaneous elimination of two OH⁻ ions and formation of a 4,5-dimethyl-1,3-dithiol-2-one in the back reaction) gives no meaningful result. Therefore, a step-wise mechanism was adopted as an alternative (as discussed for the normal ketal formation in dithiols⁴).

We find a stable intermediate (described as 2,3-dimethyl-1,4-dithio-1-carboxylate anion, **Figure S12**), in which a carboxyl group is present. The sulfur atom, at which the carboxylate group is not attached, has a high negative charge (Mulliken charge: -1.117) and is able to form a bond to the carboxylate carbon (cyclization).

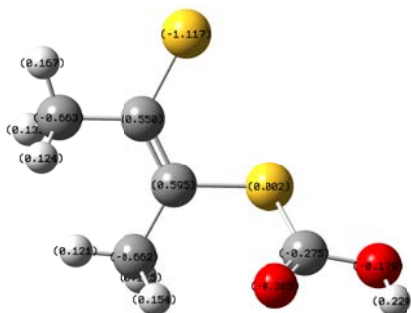


Figure S12. 2,3-dimethyl-1,4-dithio-1-carboxylate anion reaction intermediate.

The transition states of the reaction could be determined with the QST2 routine⁵ of the program in both directions: from the 2,3-dimethyl-1,4-dithio-1-carboxylate anion to the reactant (1,3-dithiol-2-one) as well as to the products (dithioanion and H₂CO₃). Transition states TS 1 and TS 2 (**Figure S13**) were confirmed by exactly one negative frequency each.

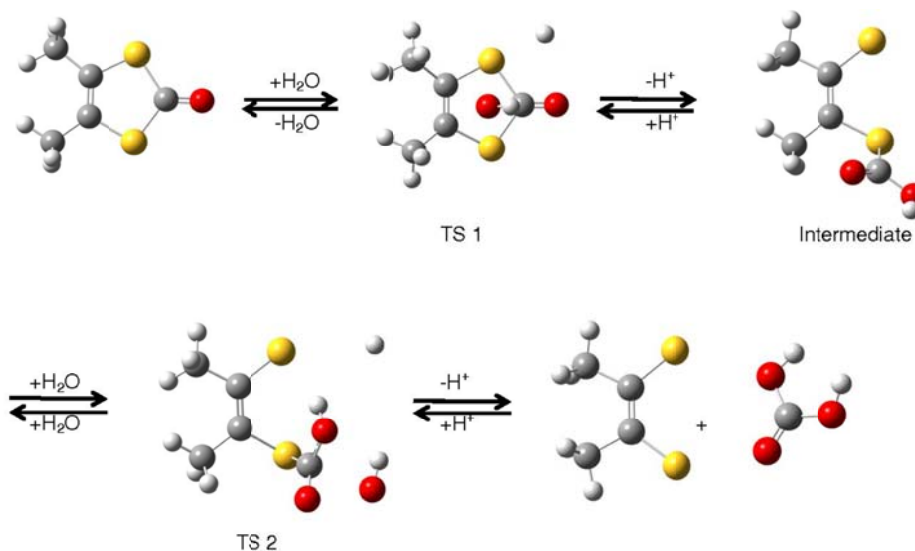


Figure S13. Proposed mechanism by DFT calculations (level of theory: B3LYP//6-311+G**) for the reformation of the 1,3-dithiol-2-one ring.

For the energy profile of the reaction, the zero-point corrected free energies of the reactants involved were determined and compared (ΔG^{298} : 298 K, 1 atm, etc.). A rational energy profile is

obtained if one takes into account that the strongly basic solutions are back-titrated with acid to neutrality.

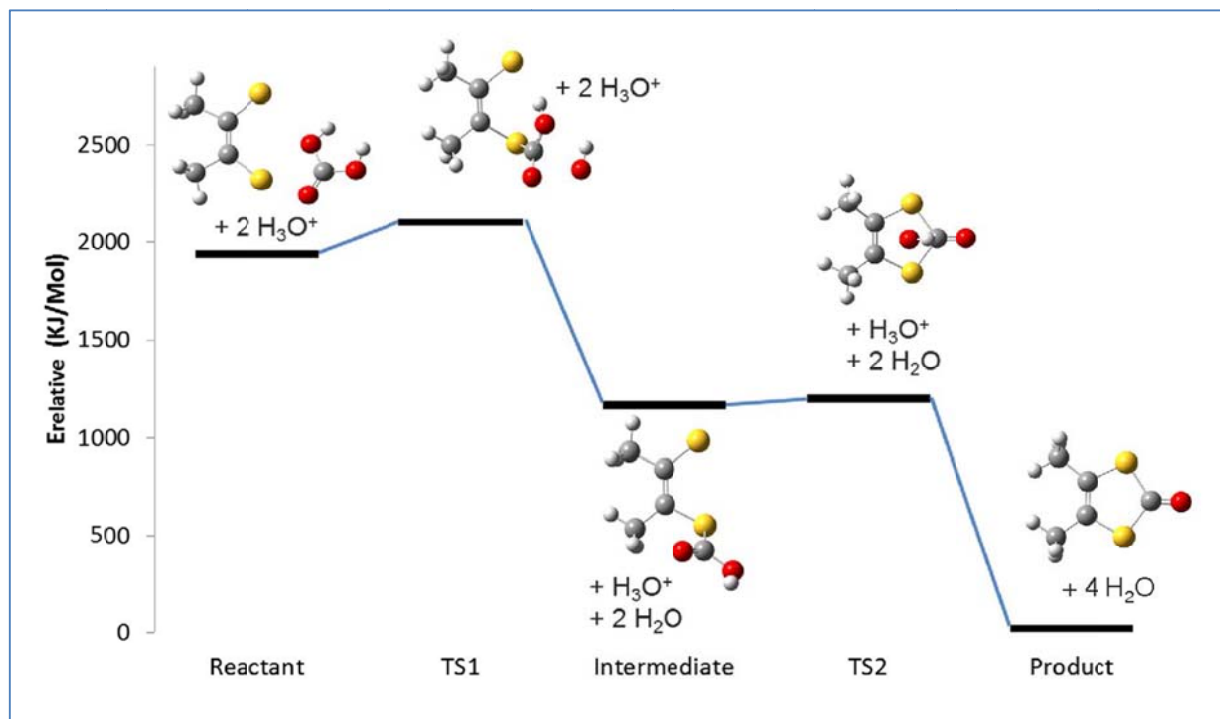


Figure S14. Calculated energy levels for proposed mechanism (level of theory: B3LYP//6-311+G**))

In course of the addition of carbonic acid to the basic solution of the dianion an OH^- ion is eliminated. This forms during further addition of acid (H^+) water – i.e. an exceptionally stable molecule. Since an H^+ ion is difficult to depict in ab initio calculation (no electron, only one proton) H_3O^+ was used instead ($\text{H}_3\text{O}^+ + \text{OH}^- \rightarrow 2 \text{H}_2\text{O}$). The same consideration applies to the formation of 1,3-dithiol-2-ones from the dithiocarboxylate anion. The titration of a solution containing H_2CO_3 and the dianion with acid leads to 1,3-dithiol-2-one and four water molecules and an energy gain of 1950.55 KJ/mol.

Overall, one can assume that corresponding to our ab initio calculations at first the carbonic acid is bound to the sulfur atom of the dianion with the loss of an OH^- anion (and subsequent formation of H_2O). During the approach of the second negatively charged sulfur anion to the electropositive carboxylate carbon atom a further bond is formed (ring closure to the five membered ring), with elimination of the second OH^- ion (and the formation of additional H_2O).

Computational Methods. Gaussian09 suite of program (RevB.01)⁶ has been used to carry out all the quantum chemistry calculations presented here. B3LYP/6-311+G(p,d)^{7,8} has been found to be a suitable method and basis set for a variety of reactions. Optimizations were carried out for the model systems in the gas phase (Convergence criteria as build in: Maximum Force < 0.000450, RMS Force < 0.000300, Maximum Displacement < 0.001800, RMS Displacement < 0.001200). In addition, normal mode vibrational frequency analyses have been performed to verify the nature of all the stationary points as either the stable minima have all positive vibrational frequencies and that the transition states have only one imaginary frequency and to compute free energies. Transition states (TS) have been located using the QST2⁵ routines as implemented in the Gaussian09 program.

Geometries:

Cartesian coordinate of OH⁻

8 0 -0.925723 0.298141 -0.896196

1 0 -1.012563 0.869888 -0.122255

Low frequency: 3754.8805 (cm^{**}-1)

ΔG^{298} HF= -75.835032 Hartree

ΔG^{298} HF= -75.966874 Hartree (Polarizable Continuum Model (PCM), Solvent: Water)

Cartesian coordinate of H₂O Free Energy in water

8 0 0.064717 0.000000 0.112093

1 0 -0.303912 0.000000 1.000735

1 0 1.018618 0.000000 0.237172

ΔG^{298} HF= -76.454823 Hartree

Low frequencies: 1602.8715 3816.9451 3922.2034 (cm^{**}-1)

Cartesian coordinate of H₃O⁺ Free Energy in water

8 0 0.000000 0.000000 0.450023

1 0 0.000000 0.000000 1.425463

1 0 0.844773 0.000000 -0.037758

1 0 -0.844773 0.000000 -0.037758

ΔG^{298} HF= -76.715101 Hartree

Low frequencies: 37.8587 1617.4869 1617.5669 (cm^{**}-1)

Cartesian coordinate of 1,3-Dimethyl-1,3-dithio-2-one

6 0 -0.961166 0.673317 0.000019

6 0 -0.961503 -0.673140 -0.000172

6 0 -2.152553 1.590516 -0.000027

6 0 -2.152939 -1.590370 -0.000030

6 0 1.632219 -0.000061 -0.000069

8	0	2.830403	-0.000404	-0.000176
16	0	0.615897	1.483635	0.000076
16	0	0.615521	-1.483604	0.000137
1	0	-2.148323	2.238856	-0.881651
1	0	-3.086875	-1.029960	0.000721
1	0	-2.149926	2.236907	0.883109
1	0	-3.086528	1.030272	-0.001379
1	0	-2.148726	-2.238178	0.881942
1	0	-2.149891	-2.236731	-0.883072

ΔG^{298} HF=-1065.816229 Hartree

Low frequencies: 89.2998 107.2949 110.8486 (cm**⁻¹)

Cartesian coordinate of 1,3-Dimethyl-1,3-dithio-dianion

6	0	-0.074801	2.524279	-0.803641
6	0	1.193222	2.646027	-0.293262
6	0	-0.880642	3.809402	-1.024321
6	0	1.695814	4.055739	0.038392
16	0	-0.956877	1.040047	-1.249183
16	0	2.386686	1.363750	0.038463
1	0	-1.186456	4.284773	-0.073299
1	0	0.985763	4.631347	0.657506
1	0	-1.789388	3.574175	-1.578838
1	0	-0.321945	4.577087	-1.587604
1	0	1.879238	4.663273	-0.868108
1	0	2.639132	3.983447	0.580501

ΔG^{298} HF= -952.395941 Hartree

Low frequencies: 52.3314 127.8723 133.0210 (cm**⁻¹)

Cartesian coordinate of TS1

6	0	0.959289	0.672947	-0.427511
6	0	0.959079	-0.672328	-0.428205
6	0	2.123752	-1.548217	-0.067653
6	0	2.124263	1.548231	-0.066512
16	0	-0.612248	-1.473669	-0.473099
16	0	-0.611893	1.474695	-0.471209
6	0	-1.583472	0.000292	-0.084790
8	0	-2.771349	0.000365	0.106005
8	0	0.044652	-0.002769	2.194155
1	0	3.077675	1.072958	-0.307390
1	0	2.081259	1.728262	1.014172
1	0	2.088378	2.510988	-0.586565
1	0	3.077334	-1.073879	-0.309740
1	0	2.086609	-2.511301	-0.586982
1	0	2.081365	-1.727444	1.013210
1	0	-0.590265	-0.002302	2.918962

ΔG^{298} HF= -1141.654829 Hartree

Low frequencies: -120.6505 61.5176 78.0551 (cm**⁻¹)

Cartesian coordinate of TS2

6	0	0.849950	0.872021	-0.295281
6	0	1.816855	-0.076516	-0.141231
6	0	1.068644	2.361874	-0.109171
6	0	3.266501	0.321433	0.129878
6	0	-1.539568	0.075859	0.861767
16	0	-0.866619	0.493609	-0.811272
16	0	1.576525	-1.829093	-0.158605
1	0	0.374465	2.748494	0.647534
1	0	3.498362	0.237860	1.200020
1	0	0.849172	2.917938	-1.032034
1	0	2.083535	2.622602	0.209504
1	0	3.514444	1.337814	-0.195754
1	0	3.925363	-0.379281	-0.389207
8	0	-3.546153	-0.554169	-1.212159
1	0	-3.085913	-1.314205	-1.589772
8	0	-2.205366	0.824132	1.529704
8	0	-1.108080	-1.100445	1.339230
1	0	-0.415433	-1.487663	0.737771

ΔG^{298} HF= -1217.457209 Hartree

Low frequencies: -52.4654 53.0381 66.3518 (cm**⁻¹)

Cartesian coordinate of Intermediate

6	0	-0.412628	0.668489	-0.669002
6	0	-0.878972	1.603989	0.218533
6	0	-1.250781	-0.185740	-1.588948
6	0	-2.396009	1.746259	0.361916
6	0	1.718614	-1.122993	-0.692152
16	0	1.349344	0.581081	-0.948720
16	0	0.076584	2.689944	1.182871
1	0	-1.048983	-1.253891	-1.448978
1	0	-2.883000	0.784475	0.562726
1	0	-1.052218	0.047113	-2.645453
1	0	-2.316483	-0.026228	-1.415776
1	0	-2.845044	2.160586	-0.550069
1	0	-2.613429	2.424916	1.184465
8	0	3.036717	-1.359982	-1.026629
1	0	3.177502	-2.295372	-0.823612
8	0	1.009030	-2.020700	-0.294548

ΔG^{298} HF= -1141.718353 Hartree

Low frequencies: 31.8321 59.1539 78.5666 (cm⁻¹)

Notes and references

1. N. Crivillers, N. Oxtoby, M. Mas-Torrent, J. Veciana and C. Rovira, *Synthesis*, 2007, **2007**, 1621-1623.
2. (a) P. Chandrasekaran and J. P. Donahue, *Org. Synth.*, 2009, **86**, 333-343; (b) P. Chandrasekaran, K. Arumugam, U. Jayarathne, L. M. Pérez, J. T. Mague and J. P. Donahue, *Inorg. Chem.*, 2009, **48**, 2103-2113.
3. (a) Cances, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* 1997, **107**, 3032–3041. (b) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, *J. Chem. Phys. Lett.* 1996, **255**, 327–335. (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* 1998, **19**, 404–417. (d) Tomasi, J.; Mennucci, B.; and Cammi, R.; (2005). *Chem. Rev.* **105(8)**: 2999-3094.
4. Lowry, T.H.; Richardson K.S. , *Mechanismen und Theorie in der Organischen Chemie*, Verlag Chemie, 1980, **451**.
5. (a) C. Peng and H. B. Schlegel, *Israel J. of Chem.*, **33**, 449 (1993). (b) C. Peng, P. Y. Ayala, H. B. Schlegel and M. J. Frisch, *J. Comp. Chem.*, **17**, 49 (1996).
6. Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.
7. McLean AD, Chandler GS (1980) *J Chem Phys* **72**:5639–5648.
8. Krishnan R, Binkley JS, Seeger R, Pople JA (1980) *J Chem Phys* **72**:650–654.